


RESEARCH PAPER



## Safety and immunogenicity of 15-valent pneumococcal conjugate vaccine compared to 13-valent pneumococcal conjugate vaccine in adults $\geq 65$ years of age previously vaccinated with 23-valent pneumococcal polysaccharide vaccine

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### ABSTRACT

**Background:** Pneumococcal disease remains a public health priority in adults. Previous studies have suggested that administration of pneumococcal polysaccharide vaccine or pneumococcal conjugate vaccine within three years following receipt of PPV23 was associated with increased reactogenicity and reduced antibody titers in comparison to longer intervals. Safety and immunogenicity of 15-valent pneumococcal conjugate vaccine (PCV15) was evaluated in adults  $\geq 65$  years of age with prior history of PPV23 vaccination (V114-007; NCT02573181).

**Methods:** A total of 250 adults who received PPV23 at least 1 year prior to study entry received a single dose of either PCV15 or PCV13 (125/arm) and were followed for safety for 14 days postvaccination. Serotype-specific Immunoglobulin G (IgG) geometric mean concentrations (GMCs) and opsonophagocytic activity (OPA) geometric mean titers (GMTs) were measured immediately prior and 30 days postvaccination.

**Results:** Safety profiles were comparable between PCV15 and PCV13 recipients. Following vaccination, serotype-specific antibody responses for the 13 shared serotypes were generally comparable between recipients of PCV15 and PCV13 for IgG GMCs, OPA GMTs, and geometric mean fold rises (GMFRs) and percentages of subjects with  $\geq 4$ -fold-rise from baseline for both IgG and OPA. Recipients of PCV15 had numerically higher antibody responses than PCV13 for two serotypes unique to PCV15 (22F, 33F).

**Conclusion:** PCV15 was generally well tolerated and induced high levels of IgG and OPA antibodies to all 15 serotypes included in the vaccine when given as a single dose to adults  $\geq 65$  years of age previously vaccinated with PPV23.

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### Introduction

Pneumococcal infection is associated with high morbidity and mortality in young children  $< 5$  years of age and adults  $\geq 65$  years of age, with the greatest burden of mortality occurring in older adults<sup>1,2</sup> Invasive pneumococcal disease (IPD) includes meningitis, sepsis/bacteremia without focus, and bacteremic pneumonia and is associated with a higher case fatality ratio than non-invasive pneumococcal disease (sinusitis, otitis media, non-bacteremic pneumonia)<sup>1–4</sup> Incidence of nonbacteremic pneumonia caused by *Streptococcus pneumoniae* is estimated to be approximately 15 times higher than IPD and represents an important etiology of community-acquired pneumonia (CAP). *S. pneumoniae* is the most common infection among older adults and approximately 400,000 hospitalizations from pneumococcal pneumonia are estimated to occur annually in the United States<sup>5</sup>

The high incidence of pneumococcal disease in adults 65 years of age and older is mainly due to waning immunity and physiological changes in the respiratory system associated with aging<sup>6</sup> In addition, age-related increase in other comorbid medical conditions such as diabetes, stroke, and susceptibility to influenza virus

infection have been shown to predispose older adults to pneumonia<sup>7–10</sup>

Adult vaccination against pneumococcal disease is recommended in many industrialized countries although vaccine uptake has remained low. Pneumococcal polysaccharide vaccines (PPVs) containing 6–23 serotypes were first developed and were shown to be efficacious against IPD in immunocompetent adults but vaccine effectiveness against nonbacteremic pneumonia varies between studies, depending on the methodology used. PPVs have been shown to be less effective in immunocompromised adults in comparison to immunocompetent adults of the same age range and ineffective in children  $< 2$  years of age due to the immaturity of their immune system. Several pneumococcal conjugate vaccines (PCVs) have been developed in order to overcome the lack of effectiveness of PPVs in children. A 7-valent PCV containing serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F (PCV7: Prevnar™, Pfizer, Philadelphia, PA) was first licensed in 2000 followed later by the licensure of 10-valent PCV (PCV-10: Synflorix™; GlaxoSmithKline, Rixensart, Belgium), and 13-valent PCV (PCV-13: Prevnar 13™, Pfizer, Philadelphia, PA)<sup>11–13</sup>

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Widespread use of PCVs has been associated with significant reduction in nasopharyngeal carriage and IPD caused by the serotypes included in these vaccines in both vaccinated children and unvaccinated individuals from other age groups (herd protection)<sup>14–20</sup>

Despite significant advances seen with PCV7 and currently licensed PCV10 and PCV13, serotype replacement remains a concern as new serotypes begin to fill the niche created by the suppression of nasopharyngeal colonization of vaccine serotypes. Notably, serotypes 22F and 33F were shown to be associated with high degree of invasiveness and IPD cases caused by these 2 serotypes have increased in both children and adults in several countries<sup>21–24</sup>

The investigational 15-valent pneumococcal conjugate vaccine (PCV15: Merck & Co., Inc., Kenilworth, NJ), contains the 13 serotypes in PCV13 (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F) plus serotypes 22F and 33F<sup>25</sup> Previous clinical studies have shown that administration of pneumococcal vaccine within three years following receipt of PPV23 was associated with increased reactogenicity and reduced antibody titers in comparison to longer intervals<sup>26–28</sup> The objective of this study (NCT02573181; V114-007) was to describe the frequency and severity of injection-site and systemic AEs, as well as immune responses (IgG and OPA) following vaccination with PCV15 or PCV13 in subjects who received PPV23 at least 1 year prior to study enrollment.

## Results

### Study population

A total of 253 subjects 65 years of age and older were given a single dose of either PCV15 (n = 127) or PCV13 (n = 126). The two vaccination groups were comparable in regard to gender, age, ethnicity/race, pre-existing conditions, prior therapy, and time intervals (1–3 years and > 3 years) since receipt of PPV23. There were fewer subjects 75 years of age or older who reported PPV23 vaccination within 1–3 years prior to study enrollment in both

vaccination groups, representing 6.3% (8/127) and 4.8% (6/126) among recipients of PCV15 and PCV13, respectively (Table 1). In both vaccination groups, all study subjects completed the protocol-specified study visits.

### Safety

The safety profile of a single dose of PCV15 was generally comparable to that of PCV13. The most commonly reported injection site and systemic AEs were those solicited on the Electronic Vaccine Report Card (eVRC). Overall, more recipients of PCV15 experienced injection-site AEs than recipients of PCV13 and the most frequent injection site AE in both groups was pain (Table 2). Nature and rates of most commonly reported systemic AEs were comparable between the 2 vaccination groups, and included fatigue (tiredness), myalgia (muscle pain), headache, and joint pain. In addition, very few subjects reported an elevated body temperature  $\geq 100.4^{\circ}\text{F}$  ( $38.0^{\circ}\text{C}$ ) (Table 2). The majority of these reported injection site and systemic events were transient (lasting 1–3 days) and reported as mild (Grade I) to moderate (Grade II) in intensity. No subject discontinued due to an AE. Two SAEs were reported (both in the active control group): acute myocardial infarction on Day 3 postvaccination and periprosthetic fracture on Day 35 (after the protocol-specified safety follow-up period). Neither of the SAEs was considered to be related to the study vaccine by the investigator and both events resolved.

### Immunogenicity

Baseline levels of serotype-specific IgG antibodies varied by serotype and were comparable between the 2 vaccine groups for all 15 serotypes include in PCV15 (Table 3). Following vaccination, serotype-specific IgG GMCs increased for all serotypes included in the respective study vaccines. The levels of serotype-specific IgG GMCs measured at 30 days postvaccination and the magnitude of antibody change from baseline

Table 1. Subject characteristics.

|  | PCV15 (%) |        | PCV13 n (%) |        | Total (%) |        |
|--|-----------|--------|-------------|--------|-----------|--------|
|  | n         | (%)    | n           | (%)    | n         | (%)    |
| Subjects in population   | 127       |        | 126         |        | 253       |        |
| <b>Gender</b>  |           |        |             |        |           |        |
| Male   | 51        | (40.2) | 51          | (40.5) | 102       | (40.3) |
| Female   | 76        | (59.8) | 75          | (59.5) | 151       | (59.7) |
| <b>Age (Years)</b>   |           |        |             |        |           |        |
| 65 to 74   | 88        | (69.3) | 89          | (70.6) | 177       | (70.0) |
| $\geq 75$  | 39        | (30.7) | 37          | (29.4) | 76        | (30.0) |
| Mean   | 72.7      |        | 72.7        |        | 72.7      |        |
| SD   | 5.8       |        | 5.7         |        | 5.8       |        |
| Median   | 72.0      |        | 72.0        |        | 72.0      |        |
| Range  | 65 to 89  |        | 65 to 96    |        | 65 to 96  |        |
| <b>Race</b>  |           |        |             |        |           |        |
| Black Or African American  | 7         | (5.5)  | 8           | (6.3)  | 15        | (5.9)  |
| White  | 120       | (94.5) | 118         | (93.7) | 238       | (94.1) |
| <b>Ethnicity</b>   |           |        |             |        |           |        |
| Hispanic Or Latino   | 20        | (15.7) | 19          | (15.1) | 39        | (15.4) |
| Not Hispanic Or Latino   | 107       | (84.3) | 107         | (84.9) | 214       | (84.6) |
| <b>Stratification†</b>   |           |        |             |        |           |        |
| Subjects 65 to 74 years of age 1 to 3 years after PPV23            | 34        | (26.8) | 34          | (27.0) | 68        | (26.9) |
| Subjects 65 to 74 years of age greater than 3 years after PPV23    | 54        | (42.5) | 55          | (43.7) | 109       | (43.1) |
| Subjects 75 years of age or older 1 to 3 years after PPV23         | 8         | (6.3)  | 6           | (4.8)  | 14        | (5.5)  |
| Subjects 75 years of age or older greater than 3 years after PPV23 | 31        | (24.4) | 31          | (24.6) | 62        | (24.5) |

†The count in each stratum is based on the age and time since prior PPV23.

**Table 2.** Adverse event summary.

|  | PCV15 |        | PCV13 |         | Total |        |
|--|-------|--------|-------|---------|-------|--------|
|  | n     | (%)    | n (%) |         | n     | (%)    |
| Subjects in population with follow-up                | 127   |        | 126   |         | 253   |        |
| with one or more adverse events                      | 87    | (68.5) | 81    | (64.3)  | 168   | (66.4) |
| injection-site                                       | 80    | (63.0) | 64    | (50.8)  | 144   | (56.9) |
| • Pain   | 73    | (57.5) | 58    | (46.0)  | 131   | (51.8) |
| • Erythema   | 12    | (9.4)  | 10    | (7.9)   | 22    | (8.7)  |
| • swelling   | 20    | (15.7) | 8     | (6.3)   | 28    | (11.1) |
| non-injection-site                                   | 50    | (39.4) | 51    | (40.5)  | 101   | (39.9) |
| • Fatigue  | 23    | (18.1) | 24    | (19.0)  | 47    | (18.6) |
| • Myalgia  | 20    | (15.7) | 14    | (11.1)  | 34    | (13.4) |
| • Joint pain   | 7     | (5.5)  | 11    | (8.7)   | 18    | (7.1)  |
| • Headache   | 17    | (13.4) | 20    | (15.9)  | 37    | (14.6) |
| with vaccine-related†AEs                             | 83    | (65.4) | 72    | (57.1)  | 155   | (61.3) |
| injection-site                                       | 80    | (63.0) | 64    | (50.8)  | 144   | (56.9) |
| non-injection-site                                   | 37    | (29.1) | 35    | (27.8)  | 72    | (28.5) |
| with serious AEs                                     | 0     | (0.0)  | 2     | (1.6)   | 2     | (0.8)  |
| with serious vaccine-related AEs                     | 0     | (0.0)  | 0     | (0.0)   | 0     | (0.0)  |
| who died   | 0     | (0.0)  | 0     | (0.0)   | 0     | (0.0)  |
| discontinued‡ due to an adverse event                | 0     | (0.0)  | 0     | (0.0)   | 0     | (0.0)  |
| discontinued due to a vaccine-related AE             | 0     | (0.0)  | 0     | (0.0)   | 0     | (0.0)  |
| discontinued due to a serious AE                     | 0     |        |       |         |       |        |
| discontinued due to a serious vaccine-related AE     | 0     | (0.0)  | 0     | (0.0)   | 0     | (0.0)  |
| Elevated body temperature (Days 1–5 postvaccination) | 125   |        |       |         |       |        |
| • < 100.4 °F (38.0 °C)                               | 2     | (98.4) | 126   | (100.0) | 251   | (99.2) |
| • ≥ 100.4 °F (38.0 °C) and < 102.2 °F (39.0 °C)      | 0     | (1.6)  | 0     | (0.0)   | 2     | (0.8)  |
| • > 102.2 °F (39.0 °C)                               |       | (0.0)  | 0     | (0.0)   | 0     | (0.0)  |

† Determined by the investigator to be related to the vaccine.

‡ Study medication withdrawn.

to 30 days postvaccination (measured by serotype-specific geometric fold-rise [GMFR] and proportion of individuals with  $\geq 4$ -fold increase) were generally comparable between recipients of PCV15 and PCV13 for the 13 shared serotypes, and higher among recipients of PCV15 than PCV13 for the 2 serotypes unique to PCV15 (22F and 33F) (Table 3). Antibody responses measured by OPA assay followed the same trends as those observed with the IgG responses (Table 4). Among recipients of PCV15 or PCV13, no notable differences in serotype-specific antibodies were observed when the study vaccine was administered within 1–3 years or more than 3 years after receipt of PPV23 (Figures 1 and 2).

## Discussion

Previous studies have suggested that repeated vaccination with PPV23 or initial vaccination with PPV23 followed by PCV13 is associated with blunted immune responses in children and adults<sup>29–32</sup> Older adults 70 years of age with prior history of PPV23 vaccination mounted a significant increase in serotype-specific OPA GMTs following administration of either PCV13 or a second dose of PPV23, but responses were higher in recipients of PCV13. In addition, individuals who received 2 doses of PCV13 had higher OPA GMTs than those who received a dose of PPV23 followed 1 year later by a dose of PCV13<sup>32</sup> Our study evaluated the safety and immunogenicity of PCV15 and PCV13 in adults 65 years of age with prior history of PPV23 vaccination and assessed the impact of the time interval between PPV23 and either PCV15 or PCV13. No differences were observed when comparing the tolerability, safety, and antibody responses between recipients of PCV15 and PCV13. The nature, incidence, and intensity of the clinical events reported by recipients of PCV15 were consistent with

previous clinical experience with currently licensed pneumococcal conjugate vaccines in the age group evaluated in this clinical trial<sup>27,32</sup> Furthermore, time interval between administrations of PPV23 and either PCV15 or PCV13 did not appear to impact the safety profiles of each vaccine and the levels of both IgG GMCs and OPA GMTs measured at 1 month postvaccination within each vaccination group. Such findings are supportive of the policy recommendation for PCV13 administration in adults  $\geq 65$  years of age with prior history of PPV23 vaccination, requiring that such individuals should receive PCV13 at least one year after PPV23.<sup>33</sup> Following vaccination, similar trends in the increases of IgG GMCs and OPA GMTs were observed, and antibody titers were comparable across the 2 vaccination groups for the shared serotypes. As expected, PCV15 induced higher IgG GMCs and OPA GMTs to serotypes 22F and 33F than PCV13.

Our study has several limitations. It was a descriptive study and was not powered to statistically compare the safety and immunogenicity of PCV15 and PCV13. Given the small number of subjects within each time interval between receipt of PPV23 and administration of either PCV15 or PCV13, no statistical analysis was performed to compare the impact of time interval (1–3 years versus  $> 3$  years) on the safety and immunogenicity of PCV15; furthermore, no formal comparison was made to analyze the impact of each time interval (1–3 years and  $> 3$  years) on the safety and immune responses between recipients of PCV15 and PCV13.

Overall, PCV15 is highly immunogenic and induces both IgG and OPA to all 15 serotypes included in the vaccine at levels comparable to PCV13 for shared serotypes. PCV15 also induced high levels of antibodies to serotypes 22F and 33F, which are not included in PCV13 and have emerged as leading causes of IPD in both children and older adults following widespread use of PCVs in many countries worldwide.

**Table 3.** Summary of IgG antibody responses (per-protocol population).

| Pneumococcal Serotype | Endpoint             | PCV15 (N = 127) |                   |                | PCV13 (N = 126) |                   |                |
|-----------------------|----------------------|-----------------|-------------------|----------------|-----------------|-------------------|----------------|
|                       |                      | n               | Observed Response | 95% CI         | n               | Observed Response | 95% CI         |
| 1                     | GMC (Day 1)          | 122             | 1.11              | (0.85, 1.45)   | 123             | 1.27              | (0.98, 1.64)   |
|                       | GMC (Day 30)         | 119             | 3.31              | (2.60, 4.23)   | 117             | 3.42              | (2.61, 4.47)   |
|                       | GMFR                 | 119             | 2.98              | (2.39, 3.73)   | 117             | 2.7               | (2.17, 3.35)   |
|                       | % $\geq$ 4-fold-rise | 119             | 32.8% (39/119)    | (24.45, 41.98) | 117             | 26.5% (31/117)    | (18.77, 35.45) |
| 3                     | GMC (Day 1)          | 122             | 0.19              | (0.15, 0.23)   | 123             | 0.19              | (0.15, 0.24)   |
|                       | GMC (Day 30)         | 119             | 0.72              | (0.57, 0.91)   | 117             | 0.46              | (0.36, 0.58)   |
|                       | GMFR                 | 119             | 3.14              | (2.54, 3.88)   | 117             | 2.03              | (1.78, 2.33)   |
|                       | % $\geq$ 4-fold-rise | 119             | 36.1% (43/119)    | (27.53, 45.45) | 117             | 17.1% (20/117)    | (10.77, 25.16) |
| 4                     | GMC (Day 1)          | 122             | 0.32              | (0.25, 0.41)   | 123             | 0.33              | (0.26, 0.43)   |
|                       | GMC (Day 30)         | 119             | 1.13              | (0.88, 1.45)   | 117             | 1.15              | (0.88, 1.51)   |
|                       | GMFR                 | 119             | 3.37              | (2.66, 4.26)   | 117             | 3.28              | (2.73, 3.95)   |
|                       | % $\geq$ 4-fold-rise | 119             | 36.1% (43/119)    | (27.53, 45.45) | 117             | 35.9% (42/117)    | (27.24, 45.29) |
| 5                     | GMC (Day 1)          | 122             | 1.31              | (1.01, 1.70)   | 123             | 1.48              | (1.14, 1.91)   |
|                       | GMC (Day 30)         | 119             | 2.69              | (2.05, 3.53)   | 117             | 3.67              | (2.75, 4.90)   |
|                       | GMFR                 | 119             | 2.14              | (1.82, 2.50)   | 117             | 2.39              | (1.97, 2.91)   |
|                       | % $\geq$ 4-fold-rise | 119             | 19.3% (23/119)    | (12.66, 27.58) | 117             | 23.9% (28/117)    | (16.53, 32.70) |
| 6A                    | GMC (Day 1)          | 122             | 0.48              | (0.36, 0.64)   | 123             | 0.47              | (0.36, 0.60)   |
|                       | GMC (Day 30)         | 119             | 3.85              | (2.77, 5.36)   | 117             | 4.34              | (3.17, 5.94)   |
|                       | GMFR                 | 119             | 7.09              | (5.71, 8.79)   | 117             | 8.24              | (6.39, 10.62)  |
|                       | % $\geq$ 4-fold-rise | 119             | 64.7% (77/119)    | (55.42, 73.24) | 117             | 65.0% (76/117)    | (55.59, 73.55) |
| 6B                    | GMC (Day 1)          | 122             | 0.64              | (0.48, 0.87)   | 123             | 0.67              | (0.52, 0.87)   |
|                       | GMC (Day 30)         | 119             | 3.74              | (2.74, 5.13)   | 117             | 3.7               | (2.72, 5.04)   |
|                       | GMFR                 | 119             | 5.2               | (4.19, 6.46)   | 117             | 4.92              | (3.90, 6.22)   |
|                       | % $\geq$ 4-fold-rise | 119             | 54.6% (65/119)    | (45.24, 63.77) | 117             | 46.2% (54/117)    | (36.90, 55.61) |
| 7F                    | GMC (Day 1)          | 122             | 1.25              | (0.94, 1.67)   | 123             | 1.01              | (0.78, 1.30)   |
|                       | GMC (Day 30)         | 119             | 3.85              | (2.96, 5.00)   | 117             | 3.24              | (2.54, 4.12)   |
|                       | GMFR                 | 119             | 2.97              | (2.44, 3.63)   | 117             | 3.03              | (2.46, 3.74)   |
|                       | % $\geq$ 4-fold-rise | 119             | 31.1% (37/119)    | (22.93, 40.23) | 117             | 33.3% (39/117)    | (24.89, 42.64) |
| 9V                    | GMC (Day 1)          | 122             | 1.26              | (0.99, 1.61)   | 123             | 1.04              | (0.84, 1.29)   |
|                       | GMC (Day 30)         | 119             | 3.79              | (2.95, 4.86)   | 117             | 2.72              | (2.17, 3.41)   |
|                       | GMFR                 | 119             | 2.98              | (2.42, 3.67)   | 117             | 2.57              | (2.18, 3.05)   |
|                       | % $\geq$ 4-fold-rise | 119             | 35.3% (42/119)    | (26.76, 44.58) | 117             | 23.9% (28/117)    | (16.53, 32.70) |
| 14                    | GMC (Day 1)          | 122             | 2.84              | (2.12, 3.81)   | 123             | 4.1               | (3.13, 5.35)   |
|                       | GMC (Day 30)         | 119             | 5.46              | (4.16, 7.17)   | 117             | 6.45              | (5.00, 8.32)   |
|                       | GMFR                 | 119             | 1.9               | (1.56, 2.32)   | 117             | 1.48              | (1.28, 1.72)   |
|                       | % $\geq$ 4-fold-rise | 119             | 18.5% (22/119)    | (11.96, 26.64) | 117             | 9.4% (11/117)     | (4.79, 16.20)  |
| 18C                   | GMC (Day 1)          | 122             | 1.69              | (1.28, 2.22)   | 123             | 1.76              | (1.38, 2.24)   |
|                       | GMC (Day 30)         | 119             | 6.85              | (5.22, 8.98)   | 117             | 5.3               | (4.15, 6.77)   |
|                       | GMFR                 | 119             | 4.06              | (3.19, 5.15)   | 117             | 2.93              | (2.37, 3.64)   |
|                       | % $\geq$ 4-fold-rise | 119             | 46.2% (55/119)    | (37.04, 55.59) | 117             | 30.8% (36/117)    | (22.57, 39.97) |
| 19A                   | GMC (Day 1)          | 122             | 3.28              | (2.54, 4.24)   | 123             | 3.29              | (2.59, 4.18)   |
|                       | GMC (Day 30)         | 119             | 9.3               | (7.32, 11.80)  | 117             | 9.41              | (7.76, 11.41)  |
|                       | GMFR                 | 119             | 2.85              | (2.32, 3.50)   | 117             | 2.81              | (2.35, 3.37)   |
|                       | % $\geq$ 4-fold-rise | 119             | 31.1% (37/119)    | (22.93, 40.23) | 117             | 35.0% (41/117)    | (26.45, 44.41) |
| 19F                   | GMC (Day 1)          | 122             | 1.46              | (1.10, 1.94)   | 123             | 1.45              | (1.12, 1.88)   |
|                       | GMC (Day 30)         | 119             | 5.06              | (3.82, 6.69)   | 117             | 4.35              | (3.35, 5.66)   |
|                       | GMFR                 | 119             | 3.37              | (2.68, 4.24)   | 117             | 2.86              | (2.36, 3.46)   |
|                       | % $\geq$ 4-fold-rise | 119             | 35.3% (42/119)    | (26.76, 44.58) | 117             | 33.3% (39/117)    | (24.89, 42.64) |
| 22F                   | GMC (Day 1)          | 122             | 0.74              | (0.57, 0.96)   | 123             | 0.68              | (0.52, 0.89)   |
|                       | GMC (Day 30)         | 119             | 2.57              | (1.97, 3.35)   | 117             | 0.6               | (0.46, 0.79)   |
|                       | GMFR                 | 119             | 3.27              | (2.62, 4.08)   | 117             | 0.9               | (0.87, 0.94)   |
|                       | % $\geq$ 4-fold-rise | 119             | 31.9% (38/119)    | (23.69, 41.10) | 117             | 0.0% (0/117)      | (0.00, 3.10)   |
| 23F                   | GMC (Day 1)          | 122             | 0.71              | (0.54, 0.93)   | 123             | 0.73              | (0.55, 0.96)   |
|                       | GMC (Day 30)         | 119             | 4.01              | (2.94, 5.46)   | 117             | 3.35              | (2.41, 4.65)   |
|                       | GMFR                 | 119             | 5.26              | (4.14, 6.68)   | 117             | 4.24              | (3.34, 5.38)   |
|                       | % $\geq$ 4-fold-rise | 119             | 52.9% (63/119)    | (43.58, 62.15) | 117             | 45.3% (53/117)    | (36.08, 54.77) |
| 33F                   | GMC (Day 1)          | 122             | 2.98              | (2.24, 3.96)   | 123             | 3.3               | (2.58, 4.23)   |
|                       | GMC (Day 30)         | 119             | 6.57              | (5.14, 8.41)   | 117             | 3.11              | (2.40, 4.04)   |
|                       | GMFR                 | 119             | 2.22              | (1.81, 2.74)   | 117             | 0.91              | (0.88, 0.95)   |
|                       | % $\geq$ 4-fold-rise | 119             | 24.4% (29/119)    | (16.97, 33.09) | 117             | 0.0% (0/117)      | (0.00, 3.10)   |

N = Number of subjects randomized and vaccinated. n = Number of subjects contributing to the analysis. CI = Confidence interval.

GMC = Geometric mean concentration ( $\mu\text{g/mL}$ ). GMFR = Geometric mean fold-rise from Day 1.

## Methods

### Study design

This was a randomized, multi-site, double-blind study comparing the safety, tolerability, and immunogenicity profiles of a single dose of either PCV15 or PCV13 in adults  $\geq 65$  years of age in good health who were vaccinated with PPV23 at least 1 year prior to study entry. It was conducted from

November 2015 through January 2016 at 17 sites in the United States. Approximately 250 subjects were randomly (1:1 ratio) assigned to either PCV15 or PCV13 vaccination group. Randomization was stratified according to subject age (65–74 years of age,  $\geq 75$  years of age [ $\sim 30\%$  of subjects]) and time since PPV23 vaccination (1–3 years,  $> 3$  years).

Serum samples collected on Day 1 prior to vaccination and on Day 30 postvaccination were assayed for vaccine-induced immune



**Table 4.** Summary of OPA antibody responses.

| Pneumococcal Serotype | Endpoint             | PCV15 (N = 127) |                   |                     | PCV13 (N = 126) |                   |                    |
|-----------------------|----------------------|-----------------|-------------------|---------------------|-----------------|-------------------|--------------------|
|                       |                      | n               | Observed Response | 95% CI              | n               | Observed Response | 95% CI             |
| 1                     | GMT (Day 1)          | 122             | 20.3              | (14.87, 27.70)      | 120             | 24.24             | (17.74, 33.12)     |
|                       | GMT (Day 30)         | 118             | 109.25            | (79.47, 150.19)     | 115             | 91.53             | (65.77, 127.37)    |
|                       | GMFR                 | 118             | 4.16              | (3.09, 5.58)        | 113             | 3.33              | (2.61, 4.25)       |
|                       | % $\geq$ 4-fold-rise | 118             | 40.7% (48/118)    | (31.73, 50.11)      | 113             | 33.6% (38/113)    | (25.01, 43.12)     |
| 3                     | GMT (Day 1)          | 122             | 23.37             | (17.56, 31.09)      | 119             | 26.71             | (19.84, 35.96)     |
|                       | GMT (Day 30)         | 117             | 145.24            | (114.93, 183.55)    | 115             | 103.77            | (81.94, 131.41)    |
|                       | GMFR                 | 117             | 5.06              | (3.92, 6.54)        | 112             | 3.24              | (2.61, 4.02)       |
|                       | % $\geq$ 4-fold-rise | 117             | 53.8% (63/117)    | (44.39, 63.10)      | 112             | 39.3% (44/112)    | (30.19, 48.96)     |
| 4                     | GMT (Day 1)          | 122             | 114.78            | (76.28, 172.72)     | 120             | 96.28             | (63.50, 145.97)    |
|                       | GMT (Day 30)         | 118             | 881.94            | (662.06, 1174.84)   | 115             | 924.82            | (706.73, 1210.21)  |
|                       | GMFR                 | 118             | 6.59              | (4.52, 9.60)        | 113             | 7.94              | (5.53, 11.40)      |
|                       | % $\geq$ 4-fold-rise | 118             | 44.1% (52/118)    | (34.94, 53.50)      | 113             | 54.9% (62/113)    | (45.23, 64.25)     |
| 5                     | GMT (Day 1)          | 122             | 41.89             | (28.38, 61.83)      | 120             | 39.52             | (26.73, 58.44)     |
|                       | GMT (Day 30)         | 118             | 183.1             | (128.24, 261.43)    | 115             | 222.18            | (154.84, 318.81)   |
|                       | GMFR                 | 118             | 3.94              | (3.01, 5.16)        | 113             | 4.95              | (3.65, 6.71)       |
|                       | % $\geq$ 4-fold-rise | 118             | 44.9% (53/118)    | (35.75, 54.34)      | 113             | 50.4% (57/113)    | (40.88, 59.98)     |
| 6A                    | GMT (Day 1)          | 121             | 71.43             | (44.92, 113.61)     | 120             | 46.57             | (29.58, 73.32)     |
|                       | GMT (Day 30)         | 118             | 2321.06           | (1632.43, 3300.19)  | 115             | 2798.09           | (2064.22, 3792.87) |
|                       | GMFR                 | 117             | 25.19             | (16.41, 38.68)      | 113             | 43.85             | (27.28, 70.49)     |
|                       | % $\geq$ 4-fold-rise | 117             | 71.8% (84/117)    | (62.73, 79.72)      | 113             | 77.0% (87/113)    | (68.13, 84.39)     |
| 6B                    | GMT (Day 1)          | 122             | 175.69            | (113.53, 271.90)    | 120             | 132.41            | (84.39, 207.76)    |
|                       | GMT (Day 30)         | 118             | 2389.2            | (1747.68, 3266.19)  | 114             | 2423.27           | (1731.26, 3391.90) |
|                       | GMFR                 | 118             | 11.83             | (8.03, 17.44)       | 112             | 14.74             | (9.85, 22.07)      |
|                       | % $\geq$ 4-fold-rise | 118             | 62.7% (74/118)    | (53.33, 71.44)      | 112             | 67.0% (75/112)    | (57.44, 75.56)     |
| 7F                    | GMT (Day 1)          | 122             | 228.75            | (150.65, 347.35)    | 119             | 205.76            | (132.00, 320.73)   |
|                       | GMT (Day 30)         | 117             | 1232.86           | (905.89, 1677.85)   | 115             | 1664.85           | (1328.78, 2085.92) |
|                       | GMFR                 | 117             | 4.77              | (3.21, 7.11)        | 112             | 7.59              | (5.03, 11.44)      |
|                       | % $\geq$ 4-fold-rise | 117             | 41.0% (48/117)    | (32.02, 50.50)      | 112             | 50.0% (56/112)    | (40.40, 59.60)     |
| 9V                    | GMT (Day 1)          | 121             | 320.81            | (221.32, 465.02)    | 119             | 222.07            | (146.84, 335.85)   |
|                       | GMT (Day 30)         | 118             | 1962.51           | (1450.32, 2655.58)  | 115             | 1387.45           | (1008.48, 1908.82) |
|                       | GMFR                 | 117             | 5.79              | (4.19, 7.99)        | 112             | 5.79              | (4.10, 8.17)       |
|                       | % $\geq$ 4-fold-rise | 117             | 47.9% (56/117)    | (38.54, 57.29)      | 112             | 44.6% (50/112)    | (35.24, 54.33)     |
| 14                    | GMT (Day 1)          | 122             | 451.24            | (312.11, 652.39)    | 120             | 475.62            | (349.01, 648.15)   |
|                       | GMT (Day 30)         | 118             | 1228.8            | (964.72, 1565.18)   | 115             | 899.66            | (683.70, 1183.84)  |
|                       | GMFR                 | 118             | 2.52              | (1.86, 3.42)        | 113             | 1.89              | (1.47, 2.42)       |
|                       | % $\geq$ 4-fold-rise | 118             | 18.6% (22/118)    | (12.07, 26.86)      | 113             | 15.9% (18/113)    | (9.72, 24.00)      |
| 18C                   | GMT (Day 1)          | 122             | 180.26            | (121.60, 267.21)    | 120             | 205.56            | (143.28, 294.93)   |
|                       | GMT (Day 30)         | 118             | 1550.65           | (1172.29, 2051.13)  | 115             | 1009.16           | (728.59, 1397.79)  |
|                       | GMFR                 | 118             | 8.14              | (5.80, 11.42)       | 113             | 4.93              | (3.61, 6.74)       |
|                       | % $\geq$ 4-fold-rise | 118             | 54.2% (64/118)    | (44.82, 63.44)      | 113             | 43.4% (49/113)    | (34.07, 53.01)     |
| 19A                   | GMT (Day 1)          | 122             | 498.71            | (352.76, 705.03)    | 120             | 480.66            | (348.91, 662.17)   |
|                       | GMT (Day 30)         | 118             | 2078.6            | (1650.03, 2618.48)  | 115             | 1861.84           | (1480.24, 2341.81) |
|                       | GMFR                 | 118             | 4.14              | (3.10, 5.53)        | 113             | 3.83              | (2.94, 5.00)       |
|                       | % $\geq$ 4-fold-rise | 118             | 37.3% (44/118)    | (28.56, 46.67)      | 113             | 37.2% (42/113)    | (28.26, 46.76)     |
| 19F                   | GMT (Day 1)          | 122             | 145.5             | (97.41, 217.32)     | 120             | 234.63            | (168.86, 326.02)   |
|                       | GMT (Day 30)         | 117             | 919.31            | (690.56, 1223.83)   | 115             | 961.71            | (747.20, 1237.79)  |
|                       | GMFR                 | 117             | 5.55              | (3.98, 7.74)        | 113             | 4.02              | (3.11, 5.19)       |
|                       | % $\geq$ 4-fold-rise | 117             | 40.2% (47/117)    | (31.22, 49.64)      | 113             | 38.1% (43/113)    | (29.08, 47.67)     |
| 22F                   | GMT (Day 1)          | 121             | 173.09            | (107.99, 277.44)    | 120             | 120.52            | (73.92, 196.49)    |
|                       | GMT (Day 30)         | 118             | 1761.25           | (1255.38, 2470.97)  | 114             | 107.83            | (64.66, 179.80)    |
|                       | GMFR                 | 117             | 8.88              | (5.44, 14.48)       | 112             | 0.85              | (0.61, 1.19)       |
|                       | % $\geq$ 4-fold-rise | 117             | 50.4% (59/117)    | (41.03, 59.80)      | 112             | 9.8% (11/112)     | (5.01, 16.89)      |
| 23F                   | GMT (Day 1)          | 122             | 69.6              | (47.54, 101.91)     | 120             | 48.74             | (31.54, 75.32)     |
|                       | GMT (Day 30)         | 118             | 846.33            | (617.56, 1159.85)   | 115             | 572.82            | (382.77, 857.23)   |
|                       | GMFR                 | 118             | 10.41             | (7.18, 15.10)       | 113             | 9.58              | (6.47, 14.19)      |
|                       | % $\geq$ 4-fold-rise | 118             | 61.0% (72/118)    | (51.61, 69.86)      | 113             | 52.2% (59/113)    | (42.61, 61.70)     |
| 33F                   | GMT (Day 1)          | 122             | 1950.86           | (1369.30, 2779.43)  | 120             | 2093              | (1416.63, 3092.30) |
|                       | GMT (Day 30)         | 118             | 7856.78           | (5750.01, 10735.45) | 113             | 2572.78           | (1800.33, 3676.67) |
|                       | GMFR                 | 118             | 3.91              | (2.76, 5.54)        | 112             | 1.03              | (0.88, 1.20)       |
|                       | % $\geq$ 4-fold-rise | 118             | 38.1% (45/118)    | (29.35, 47.53)      | 112             | 6.3% (7/112)      | (2.55, 12.45)      |

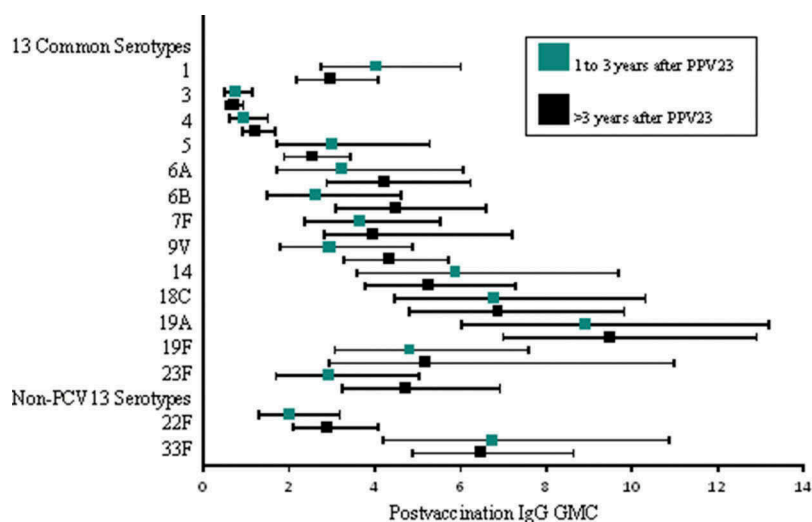
N = Number of subjects randomized and vaccinated. n = Number of subjects contributing to the analysis. CI = Confidence interval.

GMT = Geometric mean titer (1/dil).

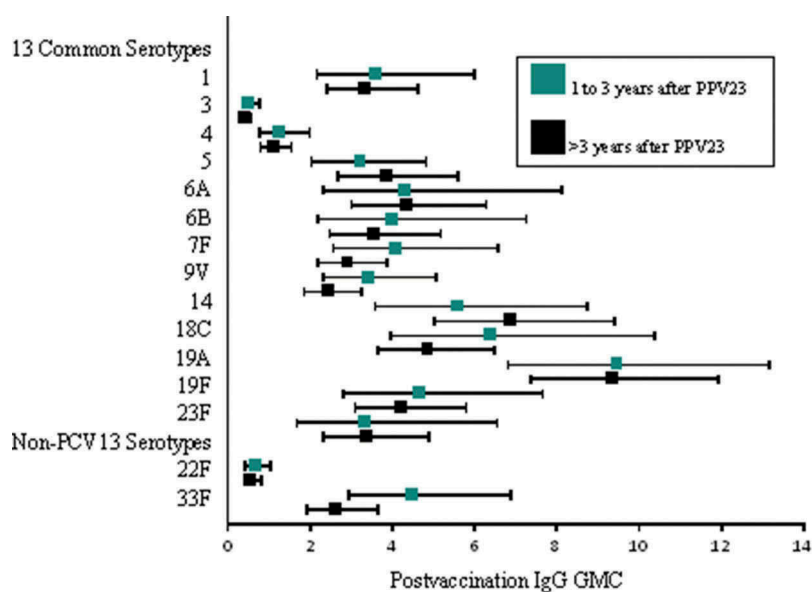
GMFR = Geometric mean fold-rise from Day 1.

responses to the 15 serotypes contained in PCV15. Primary immunogenicity endpoint was measurement of serotype-specific Immunoglobulin G (IgG) responses using pneumococcal electrochemiluminescence (Pn ECL) assay. Serotype-specific opsonophagocytic activity (OPA) using the multiplexed OPA (MOPA) assay was tested as a secondary endpoint. The Per-protocol (PP) population served as the primary population for the analysis of immunogenicity data in this study. The PP population consisted of those subjects who were not considered protocol violators.

Injection-site and systemic adverse events (AEs) were collected for 14 days postvaccination. Solicited AEs were recorded by subjects on a validated hand-held eVRC and included injection site AEs (i.e., redness, swelling, and pain/tenderness) occurring on Days 1 through 5, and systemic AEs (muscle pain, joint pain, headache, and tiredness) occurring on Days 1 through 14. Body temperature was measured orally and collected Days 1 through 5 postvaccination. Serious AEs were collected from the time the consent form was signed



**Figure 1.** Postvaccination IgG GMCs by time since PPV23 vaccination in recipients of PCV15.



**Figure 2.** Postvaccination IgG GMCs by time since PPV23 vaccination in recipients of PCV13.

through 30 days postvaccination or over the duration of the subject's participation in the study.

### Study vaccines

Subjects were randomly assigned to 1 of 2 vaccination groups: PCV15 (Lot WL00061714) or PCV13 (Lot L87117/WL00062729). The dose of PCV15 used in this trial is similar to that evaluated in the proof-of-concept clinical trial conducted in adults  $\geq 50$  years of age<sup>34</sup> PCV15 contains 2 $\mu$ g of 1, 3, 4, 5, 6A, 7F, 9V, 14, 18C, 19A, 19F, 22F, 23F, and 33F and 4 $\mu$ g of 6B; 30 $\mu$ g of CRM<sub>197</sub> and 125 $\mu$ g of aluminum phosphate adjuvant per 0.5 mL dose. PCV13 contains 2.2 $\mu$ g of 1, 3, 4, 5, 6A, 7F, 9V, 14, 18C, 19A, 19F, and 23F and 4.4 $\mu$ g of 6B; 34 $\mu$ g of CRM<sub>197</sub> and 125 $\mu$ g of aluminum per 0.5mL dose. The dose of PCV13 is consistent with the prescribing recommendation of the vaccine for adults. The timing for the administration of PCV15 or PCV13 in this study is consistent with

recommendation from the Advisory Committee on Immunization Practices (ACIP) from US Centers for Disease Control and Prevention (CDC) for adults who have previously received  $\geq 1$  doses of PPV23 but have not yet received a dose of licensed PCV13.

### Study objectives

The primary study objectives were: (1) to describe the safety and tolerability profiles of PCV15 and PCV13 when administered as a single dose in adults  $\geq 65$  years of age with a prior history of PPV23, and (2) to summarize the serotype-specific IgG responses measured at Day 1 and Day 30 postvaccination in recipients of PCV15 and PCV13 for the 13 shared pneumococcal serotypes contained in both vaccines (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F) and the 2 serotypes unique to PCV15 (22F and 33F). The secondary study objective was to summarize the serotype-specific OPA responses

measured immediately prior to vaccination at Day 1 and at Day 30 postvaccination in recipients of PCV15 and PCV13 for the 13 shared pneumococcal serotypes contained in both vaccines and the 2 serotypes unique to PCV15. The exploratory study objectives were: (1) to summarize the safety and immunogenicity (as measured by the Pn ECL assay and the MOPA assay) of PCV15 and PCV13 by time since receipt of PPV23 (1–3 years versus > 3 years) for each age cohort (65–74 years of age versus  $\geq 75$  years of age); and (2) to compare the immunogenicity (as measured by the MOPA and Pn ECL assays) at Day 30 postvaccination in recipients of PCV15 and PCV13 for the 13 shared pneumococcal serotypes contained in both vaccines and the 2 serotypes unique to PCV15.

The primary immunogenicity endpoints were the serotype-specific IgG geometric mean concentrations (GMCs) prior to vaccination at Day 1 and at Day 30 postvaccination, geometric mean fold rise (GMFR) from baseline and proportion of subjects with  $\geq 4$ -fold rise from baseline for the 15 serotypes in PCV15 based on the serotype-specific IgG responses as measured by the Pn ECL assay. The secondary immunogenicity endpoints were the OPA geometric mean titers (GMTs) prior to vaccination at Day 1 and at Day 30 postvaccination, GMFR from baseline and proportion of subjects with  $\geq 4$ -fold rise from baseline for the 15 serotypes in PCV15 based on the OPA responses as measured by the MOPA assay. For IgG GMCs/OPA GMTs and GMFR, the point estimates were calculated by exponentiating the estimates of the mean of the natural log values and the within-group confidence intervals (CIs) were derived by exponentiating the CIs of the mean of the natural log values based on the t-distribution. For the proportion of subjects with  $\geq 4$ -fold rise, the within-group CIs were calculated using the exact method for a single binomial proportion.<sup>35</sup> Additionally, estimated Day 30 IgG GMCs and 95% CIs were calculated using a constrained longitudinal data analysis (cLDA) method.<sup>36</sup>

Key safety measures for an overall assessment of safety included proportions of subjects with: (1) any adverse event (AE) through 14 days postvaccination, (2) any injection-site AE through 14 days postvaccination, (3) any systemic AE through 14 days postvaccination, (4) any SAEs through Visit 2 (~ 30 days postvaccination), (5) any vaccine-related SAEs and any deaths through Visit 2 (~ 30 days postvaccination), and (6) any discontinuation due to an AE. Other key safety parameters included proportions of subjects reporting the following solicited AEs: elevated body temperature as well as injection site swelling, redness, and pain/tenderness occurring Days 1 through 5 postvaccination, and systemic AEs of muscle pain, joint pain, headache, and tiredness occurring Days 1 through 14 postvaccination.

There were no safety hypotheses in this study. The analysis of safety results followed a tiered approach. For Tier 1 safety endpoints, point estimates, risk differences with 95% CIs and corresponding p-values are provided. Tier 2 parameters were assessed via point estimates and risk differences with 95% CIs; only point estimates by group are provided for Tier 3 safety parameters.

Tier 1 safety endpoints included solicited injection-site AEs (redness, swelling, and pain/tenderness) during Day 1 to Day 5 postvaccination, and solicited systemic AEs (muscle pain, joint

pain, headache, and tiredness) during Day 1 to Day 14 postvaccination. Temperatures collected from Day 1 through Day 5 were treated as Tier 2 events. These analyses were performed using the stratified Miettinen and Nurminen method, an unconditional, asymptotic method<sup>37</sup>. The All Subjects as Treated (ASaT) population was used in analyzing the safety endpoints. The ASaT population consisted of all randomized subjects who received at least 1 dose of study treatment.

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## Author contributors

JT Peterson and HL Stacey: enrollment of subjects and/or data collection, review of the manuscript.

JE MacNair, J Li, and P Benner: analysis and interpretation of data, and preparation of manuscript.

JS Hartzel, TM Sterling, GM Tamms, and LK Musey: study concept and design, analysis and interpretation of data, and preparation of manuscript.

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No potential conflict of interest was reported by the authors.

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